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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/320,609	05/26/99	WILUSZ J	601-1-088N

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EXAMINER	
SIU,S	
ART UNIT	**PAPER NUMBER**
1653	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/320,609	Applicant(s) WILUSZ ET AL.	
	Examiner Stephen C Siu	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-55 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-55 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☒ Other: Notice to Comply w/Sequence Rules

Application No.: 09/320,609

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIng software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

DETAILED ACTION

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

The disclosure is objected to because of the following informalities: The subsections in the figures described in the "Brief Description of the Drawings" section of the disclosure are improperly referred to as "Panel A", "Panel B", etc. All figures should be referred to by the figure number as well as any identifying letters as to the subsection. Therefore, figures should be referred to as "Fig 1A", "Fig. 1B", for example.

Appropriate correction is required.

Sequence Listing (see 37 CFR 1.821-1.825).

Sequence ID's are noted on page 63 of the specification.

The following is excerpted from the Manual of Patent Examining Procedure, Chapter 2422:

> Patent applications which contain disclosures of nucleotide and/or amino acid sequences shall, with regard to the manner in which the nucleotide and/or amino acid sequences are presented and described, conform exclusively to the requirement of §1.821 through §1.825.
>
> Patent applications which contain disclosures of nucleotide and/or amino acid sequences **must** contain, as a separate part of the disclosure, a paper copy disclosing the nucleotide and/or amino acid sequences and associated information using the symbols and format in accordance with

the requirements of §1.822 and §1.823. This paper copy is hereinafter referred to as the "Sequence Listing." Each sequence disclosed must appear separately in the "Sequence Listing." Each sequence set forth in the "Sequence Listing" shall be assigned a separate sequence identifier. The sequence identifiers shall begin with 1 and increase sequentially by integers. If no sequence is present for a sequence identifier, the code "000" shall be used in place of the sequence. The response for the numeric identifier <160> shall include the total number of SEQ ID Nos, whether followed by a sequence or by the code "000."

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with the above, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

A copy of the "Sequence Listing" referred to in the above paragraphs must also be submitted in computer readable form in accordance with the requirement of §1.824. The computer readable form is a copy of the "Sequence Listing" and will not necessarily be retained as a part of the patent application file. If the computer readable form of a new application is to be identical with the computer readable form of another application of the applicant on file in the Patent and Trademark Office, reference may be made to the other application and computer readable form in lieu of filing a duplicate computer readable form in the new application if the computer readable form in the other application was compliant with all of the requirements of these rules. The new application shall be accompanied by a letter making such reference to the other application and computer readable form, both of which shall be completely identified. In the new application, applicant must also request the use of the compliant computer readable "Sequence Listing" that is already on file for the other application and must state that the paper copy of the "Sequence Listing" in the new application is identical to the computer readable copy filed for the other application.

In addition to the required paper copy and required computer readable form, a statement that the content of the paper and computer readable copies are the same must be submitted with the computer readable form, e.g., a statement that "the information recorded in computer readable form is identical to the written sequence listing."

Compliance with the above sequence rules is mandatory prior to allowance of the case.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 7, 9-13, 15, 21-32, and 48-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 2: "C-rich element regulated turnover" is confusing because it is unclear if the turnover refers to RNA turnover of turnover of other elements.

B) Claim 7: "partially purified" is confusing because it is unclear as to the precise extent of purification.

C) Claim 9, section (c): "...inactivates a protein that bind to polyadenylate..." is confusing because it is not clear if the word "bind" refers to the protein as the word "bind" lacks the letter "s".

D) Claim 9, section (d): "that binds to polyadenylate" is confusing because there is no period at the end of the sentence.

E) Claim 10: "said extract with an material" is confusing because the noun "material" is preceded with the article "an".

F) Claim 12: "selected from the group of synthetic RNA..." is confusing because the words "consisting of" is missing for a Markush group.

G) Claim 15: "labeled with a moiety is selected..." is confusing because there appears to be missing word(s) between the words "moiety" and "is".

H) Claim 21, section (A): "providine" appears to be misspelled.

I) Claim 26, "with a moiety is selected from..." is confusing because the word "is" does not appear proper in this context.

J) Claim 27, "wherein said monitoring..." lacks proper antecedent basis. Claim 27 depends on claim 21 however, claim 21 does not recite "monitoring".

K) Claim 27, "said labeled target" lacks proper antecedent basis. Neither claim 21 nor claim 27 recite a labeled target RNA.

L) Claim 48: a dependent method claim must depend on another method claim. Claim 48 is a method claim but depends on claim 19, a claim to a system, thus rendering this claim ambiguous.

M) Claim 51, section (B): "introducing said protein" lacks proper antecedent basis. Claim only recites "endogeneous molecule" and not "protein".

N) Claim 55, "...the degradation a target..." is confusing. There appears to be at least one word omitted.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 8-10, 12-15, 21, 24-30 and 51-52 are rejected under 35 U.S.C. 102(b) as being anticipated by Bernstein.

Bernstein demonstrates the use of an in vitro mRNA decay system comprising cell extract and mRNA, the mRNA being polyadenylated. The cell extract was depleted of functional poly(A)-binding protein in two separate methods. One method of depleting the activity of the protein was by adding excess competitor poly(A) mRNA to the reactions and the other was by passing the cell extract through a poly(A)-Sepharose column (page 661, column 1, last line). The competitor poly(A) sequestered the protein so that little or none was available to interact with labeled mRNAs (page 661, column 2, top). In a related experiment, antibody to the protein was added in an attempt to block formation of the poly(A)-protein complex (page 663, column 2, top). The addition of antibody to the protein resulted in increased instability of the mRNA (page 663, column 2) by interfering with the stabilization effect of the poly(A) binding protein with poly(A).

Competitor poly(A) was added in one experiment and mRNA became destabilized. To test if exogenously added PABP could restabilize the mRNA, cytoplasmic PABP was purified from an E.coli strain and added to the system after competitor poly(A) had been added. The result was restored stability of the mRNA (page 661, column 2, "Yeast cytoplasmic PABP overcomes the destabilizing effect of competitor poly(A)).

Bernstein also demonstrated the addition of an agent (exogenous poly(A)-binding-protein) to the system to observe stabilizing effects. Cytoplasmic protein purified from E.coli was used. It was found that addition of this agent led to stability of the mRNA (page 662, column 1). This was shown to be caused by binding of the poly(A)-binding-protein to the poly(A) of the mRNA and conferring stability.

Bernstein anticipates the claimed invention because, as in the claimed invention, the mRNA decay system taught by Bernstein comprises cell extract and target RNA wherein the target RNA is polyadenylated (claims 1-2). Bernstein depleted the cell extract of the activity of poly(A)-binding protein (claim 8) by various methods which included the addition of competitor RNA and passing the extract through a poly(A)-Sepharose column. In one experiment, Bernstein adds antibody to the protein to prevent interaction of the protein with poly(A) (claims 9-11). The mRNA used was labeled with 32P to analyze degradation (claims 14-15). Bernstein adds the endogenous poly(A) binding protein exogenously to the system and observes the effect on degradation of the mRNA (claims 21, 24-27 and 51-52). This resulted in increased stability of the RNA (claim 28). However, addition of antibody to the poly(A) binding protein prevented the stabilization effect of the protein through modulation of activity of the poly(A) element and therefore resulted in decreased stability of the RNA (claim 29). Further, to test the effect on mRNA stability by exogenously added PABP, Bernstein first introduced competitor poly(A) RNA ("RNA stability modifier"), then introduced exogenous PABP ("agent"), then determined the extent of turnover of the target RNA

and identified the exogenous PABP ("agent") as capable of modulating the stability of the RNA in the presence of the previously introduced competitor poly(A) RNA (claims 33, 36-40, and 43).

Claims 1, 3-7, 12, 14, 16-17, 21-25, 28 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Krikorian.

The claims are drawn to an in vitro system of "recapitulating" RNA turnover of exogenously added target RNA. This system comprises a cell extract prepared from lysed HeLa cells that have been infected. The cell extract is "partially purified" and the target RNA sequence is synthetic RNA, naturally occurring RNA, mRNA, chemically modified RNA or RNA-DNA derivatives. Exogenously added ATP may also be added to the system. Claims are also drawn to a method of identifying an agent that modulates RNA stability that uses the system described above in which said agent is added to the system and subsequent turnover of RNA is observed.

Krikorian teaches an in vitro mRNA degradation system that examines RNA turnover of endogenous and exogenously added target RNA (pg117, column 2, 2nd paragraph). This system comprises a cell extract of lysed HeLa cells (page 113, 1st column, "Materials and Methods" section) and exogenously added GAPD mRNA as the target mRNA. The HeLa cells were infected with stocks of wild-type HSV-1 strain KOS and mutant vhs1 (virion host shutoff). Cytoplasmic extracts were prepared from infected HeLa S3 cells (page 114, column 2, "strategy" section). In testing if pretreatment with

micrococcal nuclease would inactivate the in vitro vhs activity, degradation extracts from HeLa cells after infection with wild-type HSV-1 was obtained (page 117, column 1, 3rd paragraph). After micrococcal nuclease and CaCl2 were added, EGTA was added to chelate the Ca+2 and inactivate the micrococcal nuclease (micrococcal nuclease sequesters endogenous mRNAs from the extract). The extracts were then supplemented with total cytoplasmic RNA and analyzed for in vitro decay of exogenous GAPD mRNA after incubation (Page 117, column 2, 1st paragraph). Krikorian also performed various experiments to determine if certain factors or compounds could alter the virion host shutoff gene (and hence mRNA stability) in vitro. Experiments were conducted by adding proteinase K, Mg+2, K+, etc (page 117, 1st column, 2nd paragraph) and noting the subsequent stability (e.g., degradation) of mRNA to determine if the addition of these agents had any effect on the stability of the mRNA. Proteinase K led to increased stability of the mRNA (abolished vhs-mediated in vitro degradation) (page117, column 1, lines 11-12 of second paragraph). In another experiment, energy components, such as ATP, GTP, creatine phosphate and creatine phosphokinase were included in the mRNA decay system. Results indicated that the addition of ATP, GTP, creatine phosphate, or creatine phosphokinase did not affect the mRNA degradative activity of the virion host shutoff gene instability (page 119, second column, line 15).

The in vitro mRNA stability testing system of Krikorian anticipates the claims because, as claimed in the present invention, the system of Krikorian comprises a cell extract and target RNA (claim 1), the RNA is messenger RNA (claim 12 and 14) and the

cell extract is isolated from lysed HeLa cells (claims 3 and 4), cells are transfected with foreign nucleic acid (claims 5 and 6) and cell extract is "partially" purified (claim 7). Krikorian tests the effects of the addition of ATP, GTP, creatine phosphate, or creatine phosphokinase (claim 17). The system as described by Krikorian entails the addition of agents into the mRNA stability testing system described above and determining the extent of turnover of the RNA sequence in question (claims 21 and 25) in the presence and in the absence of ATP, GTP, creating phosphate, or creatine phosphokinase (claims 22-23 and 55). One of the agents examined in Krikorian's system was proteinase K which modified the stability of mRNA molecule (claim 24), in particular, resulted in increased stability of the mRNA molecule (claim 28).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-32 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein in view of Chen and in further view of any one of Zhang, Myer, Nakagawa, Levine, Nagy, Nakamaki, or Liu.

Bernstein teaches an in vitro system and method for evaluating mRNA stability. Poly(A) binding proteins are added to a system of mRNA and cell extract and the resulting effects on mRNA stability are observed. Bernstein examines "PABP" – Poly(A) Binding Protein, which is a protein that binds to the poly (A) element on the mRNA to affect the stability of the mRNA.

Bernstein does not demonstrate the role of other RNA binding proteins in mRNA stability.

Chen describes inhibitors that inhibit mRNA decay. AU-A and hnRNP A1 proteins were observed in the cytoplasm after treatment of cells with Actinomycin D or DRB. Both of these proteins had been shown to bind to AREs in studies. Chen states that several other ARE-binding proteins were also found in the cytoplasm and nucleus and further explains the disruption of functional ARE-protein complex formation leading to mRNA stabilization

Chen does not describe other RNA binding proteins affecting mRNA stability.

Zhang teaches the binding of AUF1, an AU-rich element RNA-binding protein to and AU-rich element in the 3' untranslated region of mRNAs and provides data on the role of this protein in mediating ARE-directed mRNA degradation.

Myer teaches the binding of HuR to mRNA as a protein in AUUUA-mediated mRNA decay. HuR is shown to bind selectivity to the AU-rich element in mRNA and play a role in the regulation of mRNA degradation.

Nakagawa teaches AUH, a gene that codes a protein that binds specifically to AU-rich transcripts.

Levine teaches Hel-N1, an RNA-binding protein with 3' UTR mRNA specificity and requiring a sequence containing AUUUG, AUUUA, and GUUUUU.

Nagy teaches glyceraldehyde-3-phosphate dehydrogenase, a protein that selectively binds AU-rich RNA and suggests its role in the regulation of ARE-dependent mRNA turnover.

Nakamaki teaches hnRNP C and AUF1 as AU-rich element binding proteins and determines that AU-binding fcators, including hnRNP C and AUF1, may be involved in rapid degradation of mRNA transcripts.

Liu teaches Hu antigens coded by HuD, HuC and Hel-N1 genes are homologues of Elav proteins and bind to AU-rich elements of mRNAs that regulate cell proliferation.

One of ordinary skill in the art would have been motivated to evaluate the effect of additional ARE RNA binding proteins in the system of evaluating mRNA deadenylation and degradation because the system had been used earlier for evaluating one such protein by Bernstein with the conclusion at that time that ARE RNA binding proteins affected mRNA stability. Further, Chen described a potential mechanism for altering mRNA stability by proteins that bind to the ARE of mRNA and cites two proteins in particular (AU-A and hnRNP A1) that have affinities for the ARE of mRNA and alter mRNA stability. The mRNA instability system and method of Bernstein was used for analyzing the effect of binding proteins and analysis on PABP (poly(A)

binding proteins) was performed. Zhang, Myer, Nakagawa, Levine, Nagy, Nakamaki, and Liu each demonstrate the binding patterns of various RNA binding proteins (AU-A, hnRNP A1, AUF1, HuR, AUH, Hel-N1, Glyceraldehyde-3-phosphate dehydrogenase, hnRNP C, HuD, and HuC) and their roles in binding to ARE of mRNA and affecting mRNA stability. It would have been prima facie obvious to one or ordinary skill in the art to utilize the system and method outlined by Bernstein wherein an RNA binding protein that binds to ARE in mRNA was analyzed as to its effects on mRNA stability and test other known RNA binding proteins that have the same function as the protein analyzed by Bernstein.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to perform the claimed invention.

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein in view of Brewer and in further view Krikorian.

Bernstein demonstrates a system and method for evaluating the effect of exogenously added agents (PABP) on the stability of poly(A) mRNAs. A system comprising target RNA and cell extract depleted of poly(A) binding protein is utilized wherein exogenous PABP is introduced into the system and the effect of PABP on the resulting degradation of mRNA is evaluated. Bernstein further states that "inhibitors that interfere with polyadenylation can affect other ATP-dependent processes..." thus

indicating that ATP-dependent processes are performed in the process of mRNA degradation.

Bernstein does not teach the monitoring of deadenylation and degradation of target RNA and does not explicitly teach the relationship between deadenylation and degradation of target mRNA.

Brewer demonstrates a system and method for monitoring deadenylation and degradation of target RNA and teaches that poly(A) shortening precedes degradation of mRNA with AU-rich sequences at the 3' end.

Brewer does not specifically teach the addition of nucleotide triphosphate to the system of mRNA turnover.

Krikorian demonstrates the use of an in vitro mRNA degradation system, the system comprising target mRNA and cell extract. In an experiment to determine whether virion host shutoff-induced in vitro mRNA degradation was dependent upon the components of an energy-generating system, parallel in vitro degradation experiments were conducted in which half of the reactions contained all of the components of the standard reaction, including ATP, GTP, etc, and the other half did not contain these elements. The degradation of mRNA was then observed.

One of ordinary skill in the art would have been motivated to utilize a system of evaluating mRNA decay in the presence of a nucleotide triphosphate, then introduce an agent to evaluate the ensuing effects on the deadenylation and degradation on the target RNA because Brewer taught that polyadenylation of the mRNA precedes

degradation of the RNA and Bernstein had earlier described and utilized a system of evaluating exogeneously introduced agents introduced into the system and observing the resulting effect on mRNA stability by monitoring the degradation of the mRNA. Krikorian had also demonstrated the use of such a system to evaluate mRNA degradation in the presence of ATP, GTP, etc. Bernstein further teaches that polyadenylation is an ATP-dependent process and indicates the presence of other ATP-dependent processes present in the procedure and Krikorian demonstrates the use of ATP, GTP, etc. in the performance of evaluation of mRNA turnover in his system. One of ordinary skill in the art, knowing the sequence of events in mRNA degradation, i.e., deadenylation preceding degradation, also knowing that ATP-dependent steps are present in the process as per the teachings of Bernstein, and following the teachings of Brewer in evaluating deadenylation and degradation of mRNA, would have utilized the system taught by Bernstein of evaluating mRNA deadenylation and degradation as well as first introducing a nucleotide triphosphate (ATP) as an energy source of required energy for ATP-dependent steps in the process since Bernstein had taught of the need for ATP and Krikorian had demonstrated such a use of ATP in an in vitro system to evaluate mRNA turnover.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have performed the claimed invention.

Claim 53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernstein.

The claims are drawn to a kit comprising cell extract depleted of activity of proteins that bind poly(A) and other reagents.

Bernstein utilized a system in which poly(A) mRNA stability was evaluated. Cell extract was depleted of poly(A) binding protein since RNA binding proteins that bind to ARE of mRNA was known to affect the stability of the mRNAs. Using both competitor RNA to sequester the poly(A) binding protein and a process of passing the extract through a column of material that depletes the extract of the macromolecules, the poly(A) binding protein was removed from the solution. In another experiment, antibodies were introduced into the extract to bind to the protein, thus preventing interaction between the protein and poly(A).

One of ordinary skill in the art would have been motivated to package the cell extract and reagents of Bernstein into a kit because it was well-known and common knowledge in the art to package together reagents into a kit to facilitate practice of methods requiring said agents.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to practice the claimed invention.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Siu whose telephone number is (703) 308-7522.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Correspondence related to this application may be submitted to Group 1653 by facsimile transmission. This faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). **Official communications should be directed to the Technology Center 1600 fax number (703) 308-4242.** Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP ~~1800~~ 1600 10/28/99

Kenneth R. Horlick, Ph.D.

Stephen Siu

Patent Examiner